

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number  
**WO 2004/004692 A1**

(51) International Patent Classification<sup>7</sup>: A61K 9/14,  
9/20, 31/165

(74) Common Representative: RANBAXY LABORATO-  
RIES LIMITED; c/o DESHMUKH, Jay R., 600 College  
Road East, Suite 2100, Princeton, NJ 08540 (US).

(21) International Application Number:

PCT/TB2003/002693

(22) International Filing Date: 8 July 2003 (08.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
723/DEL/2002 8 July 2002 (08.07.2002) IN

(71) Applicant (for all designated States except US): RAN-  
BAXY LABORATORIES LIMITED [IN/IN]; 19, Nehru  
Place, 110 019 New Delhi, Delhi (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): SINGH, Romi,  
Barat [IN/IN]; A-14, Badshah Bagh, 221002 Varanasi,  
Uttar Pradesh (IN). KUMAR, Pananchukunnath, Manoj  
[IN/IN]; 25 Laxmi Vihar Apartments, Block H-3, Vikas  
Puri, 110018 New Delhi, Delhi (IN). NAGAPRASAD,  
Vishnubhotla [IN/IN]; 102, Surya Niwas Apartments,  
Balaji Nagar, 500072 Kukatpally, Hyderabad (IN). ROY,  
Sunilendu, Bhushan [IN/IN]; Bungalow #7, Row House,  
Lokpuram, Than, 400601 Mumbai, Maharashtra (IN).  
MALIK, Rajiv [IN/IN]; 6-B, Pocket-B, Gangotri Enclave,  
Alaknanda, 110019 New Delhi, Delhi (IN).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,  
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,  
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: PROCESSES FOR THE PREPARATION OF ORAL DOSAGE FORMULATIONS OF MODAFINIL

(57) Abstract: The invention relates to processes for preparing, and pharmaceutical compositions of, modafinil dosage forms for oral administration. The dosage forms include a mixture of coarse and fine particles of modafinil. The process for preparing modafinil oral dosage forms includes forming a dosage form that includes about 7% - 25% by weight of modafinil particles having diameters greater than 220 µm and about 75% - 93% by weight of modafinil particles having diameters less than 220 µm.

WO 2004/004692 A1

## PROCESSES FOR THE PREPARATION OF ORAL DOSAGE FORMULATIONS OF MODAFINIL

### Field of the Invention

The technical field of the invention relates to processes for preparing, and  
5 pharmaceutical compositions of, modafinil dosage forms for oral administration. The dosage forms include a mixture of coarse and fine particles of modafinil.

### Background of the Invention

Modafinil is a wakefulness-promoting agent indicated for use in narcolepsy and idiopathic hypersomnia. It also is used for improving memory and mood. Compared to  
10 amphetamines and methylphenidate, modafinil is less likely to cause jitteriness, anxiety, or excess locomotor activity. The precise mechanism of action is not fully understood but it is thought to modulate the central postsynaptic  $\alpha_1$ -adrenergic receptors. However, modafinil has a different pharmacokinetic profile compared to the sympathomimetic agents, such as amphetamines and methylphenidate.

15 The benzhydrylsulfinyl acetamide structure of modafinil makes it insoluble in water (less than 1 mg/ml) as well as unstable at higher temperatures. These physicochemical properties decrease the drug's potential for abuse via injection or smoking, and lead to reduced cases of dependency compared to amphetamines.

Over the years, more than 40% of the potential candidates in drug discovery and  
20 research have failed to emerge as drugs due to their poor biopharmaceutic properties. Most of these are rejected due to poor solubility characteristics and further development is continued only if the new molecule has some marked advantage over the existing molecules indicated for the similar use.

The most common approach used to address the problem of insolubility is by either  
25 reducing the drug's particle size or micronizing the drug to the size of a few microns, which increases the effective exposed surface area. Dosage forms which contain micronized drug particles exhibit enhanced solubility and consequently an increase in the bioavailability of the drugs. However, technical and economical problems can arise. For example, highly micronized drug particles possess poor flow properties and an increased

chance of re-agglomeration during processing. In some cases, re-agglomeration of micronized drug particles may be so problematic that the basic objective of enhancing the solubility by increasing the effective surface area may be unmet.

- 5 U.S. Patent No. RE 37,516 discloses a method of size reduction and a pharmaceutical composition that has at least 95% of the modafinil particles having a diameter of less than 200  $\mu\text{m}$ .

### **Summary of the Invention**

10 In one general aspect, there is provided a pharmaceutical composition of modafinil that includes a combination of coarse and fine particles of modafinil.

In another general aspect there is provided a process for preparing an oral dosage form containing modafinil. The process includes forming a dosage form that includes about 7% - 25% by weight of modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 93%- 75% by weight of modafinil particles have diameters less than 220  $\mu\text{m}$ .

15 Embodiments of the process of forming the oral dosage form may include one or more of the following features. For example, forming a dosage form may further include mixing the modafinil particles in geometric progression with one or more pharmaceutically acceptable excipients to form a blend. Forming a dosage form may still further include granulating the blend to form granules, optionally drying the granules,  
20 sizing the granules, mixing the sized granules with one or more extragranular pharmaceutically acceptable excipients, and compressing into a tablet.

Forming the dosage form may further include blending the modafinil particles with one or more pharmaceutically inert excipients to form a blend, granulating the blend to form granules, blending the granules with one or more pharmaceutically inert excipients,  
25 and compressing or filling into a solid dosage form. Granulating may be wet granulation or dry granulation. The dosage form may be a tablet and the process may further include coating the tablet.

Forming the dosage form also may further include blending the modafinil particles with one or more pharmaceutically inert excipients to form a blend and compressing the  
30 blend or filling the blend into a solid dosage form.

Of the dosage form, about 7% by weight of the modafinil particles may have diameters greater than 220  $\mu\text{m}$  and about 93% by weight of the modafinil particles may have diameters less than 220  $\mu\text{m}$ . About 10% by weight of the modafinil particles may have diameters greater than 220  $\mu\text{m}$  and about 90% by weight of the modafinil particles may have diameters less than 220  $\mu\text{m}$ . About 15% by weight of the modafinil particles may have diameters greater than 220  $\mu\text{m}$  and about 85% by weight of the modafinil particles may have diameters less than 220  $\mu\text{m}$ . The specific surface area of the modafinil particles may be at least 0.2  $\text{m}^2/\text{gm}$ . The dosage form may release at least 75% of the modafinil in about 45 minutes.

The oral dosage form may be a tablet or a capsule and the tablet is formed by either wet granulation, dry granulation, or direct compression. The process may further include coating the tablet.

The dosage form may include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may be one or more of binders, diluents, disintegrants, surfactants, lubricants, glidants, and coloring agents.

In another general aspect, there is provided an oral dosage form of modafinil including about 7% to 25% by weight of modafinil particles having diameters greater than 220  $\mu\text{m}$  and about 93% to 75% by weight of modafinil particles having diameters less than 220  $\mu\text{m}$ . The dosage form releases at least 75% of the modafinil in about 45 minutes.

Embodiments of the dosage form may include one or more of the following features. For example, about 7% by weight of the modafinil particles may have diameters greater than 220  $\mu\text{m}$  and about 93% by weight of the modafinil particles may have diameters less than 220  $\mu\text{m}$ . About 10% by weight of the modafinil particles may have diameters greater than 220  $\mu\text{m}$  and about 90% by weight of the modafinil particles may have diameters less than 220  $\mu\text{m}$ . About 15% by weight of the modafinil particles may have diameters greater than 220  $\mu\text{m}$  and about 85% by weight of the modafinil particles may have diameters less than 220  $\mu\text{m}$ . The specific surface area of the modafinil particles may be at least 0.2  $\text{m}^2/\text{gm}$ .

The oral dosage form may be a tablet or capsule. The oral dosage form may further include one or more pharmaceutically acceptable excipients. The pharmaceutically

acceptable excipients may be one or more of binders, diluents, disintegrants, surfactants, lubricants, glidants, and coloring agents.

In another general aspect, there is provided a method of treating a condition using modafinil. The method of treating includes providing an oral dosage form of modafinil  
5 that includes about 7% to 25% by weight of modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 93% to 75% by weight of modafinil particles have diameters less than 220  $\mu\text{m}$ . The dosage form releases at least 75% of the modafinil in about 45 minutes.

Embodiments of the method of treating with modafinil may include one or more of the following features. For example, the condition may be one or both of narcolepsy and  
10 idiopathic hypersomnia.

Of the dosage form, about 7% by weight of the modafinil particles may have diameters greater than 220  $\mu\text{m}$  and about 93% by weight of the modafinil particles may have diameters less than 220  $\mu\text{m}$ . About 10% by weight of the modafinil particles may have diameters greater than 220  $\mu\text{m}$  and about 90% by weight of the modafinil particles  
15 may have diameters less than 220  $\mu\text{m}$ . About 15% by weight of the modafinil particles may have diameters greater than 220  $\mu\text{m}$  and about 85% by weight of the modafinil particles may have diameters less than 220  $\mu\text{m}$ . The specific surface area of the modafinil particles may be at least 0.2  $\text{m}^2/\text{gm}$ .

The oral dosage form used to treat the condition may be a tablet or capsule. The  
20 oral dosage form may further include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may be one or more of binders, diluents, disintegrants, surfactants, lubricants, glidants, and coloring agents.

In another general aspect, there is provided an oral dosage form that includes an intragranular portion and an extragranular portion. The intragranular portion includes  
25 about 7% to 25% by weight of modafinil particles having diameters greater than 220  $\mu\text{m}$ , about 93% to 75% by weight of modafinil particles having diameters less than 220  $\mu\text{m}$ , and one or more pharmaceutically acceptable excipients. The extragranular portion includes one or more pharmaceutically acceptable excipients.

Embodiments of the oral dosage form may include one or more of the following  
30 features. For example, the oral dosage form may release one or more of between 48% and

81% of the modafinil within 15 minutes, between 68% and 87% of the modafinil within 30 minutes, between 76% and 95% of the modafinil within 45 minutes, between 84% and 97% of the modafinil within 60 minutes, and between 89% and 98% of the modafinil within 90 minutes. The modafinil is released in a USP Apparatus II, in 900 ml of water, and stirred at 50 rpm. The oral dosage form may be provided with labeling for one or more of wakefulness promotion, to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, and idiopathic hypersomnia.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects, and advantages of the invention will apparent from the description and the claims.

### **Detailed Description of the Invention**

The inventors have recognized that there is an unmet need for a simple, cheaper, and faster process of preparing modafinil dosage forms having an improved dissolution rate without the processing problems of the prior art. In particular, the inventors have now discovered that the problem of reagglomeration of micronized modafinil particles can be avoided by mixing coarse particles (diameters greater than 220  $\mu\text{m}$ ) and fine particles (diameters less than 220  $\mu\text{m}$ ) in a ratio of between about 7:93 to about 25:75 by weight. The combination of coarse and fine particles of the drug improves the flow properties of the composition and thereby facilitates the processing of the dosage form with reduced problems of reagglomeration. Further, the use of a combination of coarse and fine particles reduces the problem of drug loss and improves the homogeneity of the drug particles. The present process also provides a dosage form with almost total drug release within 60 to 90 minutes.

Recognizing the above problems, the inventors have developed processes for preparing modafinil oral dosage forms in which about 7% to 25% by weight of the modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 75% to 93% by weight of the modafinil particles have diameters less than 220  $\mu\text{m}$ . Additionally, the dosage form made by these processes release at least 75% of the drug in about 45 minutes.

As used herein the term "coarse" means modafinil particles having diameters greater than 220  $\mu\text{m}$  and the term "fine" means modafinil particles having diameters less than 220  $\mu\text{m}$ . A particularly suitable mean particle size of fines is that of diameters less

than 180  $\mu\text{m}$ . An even more suitable mean particle size of fines is that of diameters less than 60  $\mu\text{m}$ . The ratio of coarse and fine particles may vary from about 7:93 to 25:75 by weight. Variations within this range generally do not affect the dissolution profile of this modafinil dosage form. Preferably, the specific surface area of the combined coarse and fine modafinil particles is at least 0.2  $\text{m}^2/\text{gm}$ . The particle sizes are determined using, for example, a Malvern Master Sizer or by sieve analysis.

The term 'pharmaceutical composition' as used herein includes solid dosage forms such as tablet, capsule, pill and the like. These dosage forms may be prepared by processes known in the art including, for example, comminuting, mixing, granulating, melting, sizing, filling, drying, molding, immersing, coating, compressing, etc.

The desired modafinil particle size may be obtained by conventional methods, such as milling and sieving. Methods of comminuting the modafinil particles may include air jet milling, multi-milling, ball milling or any other method of particle reduction.

In one of the embodiments, the pharmaceutical composition of modafinil is prepared by a wet granulation process that includes the steps of blending coarse and fine modafinil particles with one or more intragranular pharmaceutically inert excipients to form a blend; wet granulating the blend with a granulating fluid or solution/dispersion of one or more pharmaceutically inert excipients in the granulating fluid to form granules; drying and sizing the granules; optionally blending the dried and sized granules with one or more pharmaceutically inert extragranular excipients; and compressing that blend into tablets or filling that blend into capsules. The pharmaceutical composition may optionally be coated with or more functional and/or non-functional coatings.

In another embodiment, the pharmaceutical composition of modafinil is prepared by a dry granulation process that includes the steps of blending coarse and fine modafinil particles with one or more intragranular pharmaceutically inert excipients to form a blend; dry granulating the blend by roller compactor or slugging to form granules; sizing the granules; optionally blending the sized granules with one or more pharmaceutically inert extragranular excipients to form a blend; and compressing that blend into tablets or filling that blend into capsules. The pharmaceutical composition may optionally be coated with or more functional and/or non-functional coatings.

In yet another embodiment, the pharmaceutical composition of modafinil is prepared by a direct compression process that includes the steps of blending coarse and fine modafinil particles with one or more pharmaceutically inert excipients to form a blend and then compressing the blend into tablets or filling the blend into capsules. The  
5 pharmaceutical composition may optionally be coated with or more functional and/or non-functional coatings.

The pharmaceutical composition also may be prepared by mixing the coarse and the fine modafinil particles in geometric progression with filler(s) and disintegrant(s); wet granulating the blend with an aqueous solution of binder; drying and sizing the granules;  
10 and compressing the granules into a tablet.

Mixing solid ingredients in a geometric progression generally refers to a process of adding almost equal amounts of two ingredients and then mixing to form a homogenous mixture of the two. This process is repeated by further mixing equal amounts to the mixture until the entire first ingredient is consumed. The entire mixture then is divided  
15 into, for example, four equal proportions and small amounts are taken from each portion and mixed thoroughly. This mixing is continued by adding from each portion until all the portions are completely used. The mixture then is further divided into two portions and the above process is repeated and ultimately the entire mixture is mixed randomly.

The term "pharmaceutically acceptable inert excipients" as used herein includes all  
20 excipients used in the art of manufacturing solid dosage forms. Examples include binders, diluents, disintegrants, surfactants, lubricants/glidants, coloring agents, and the like.

Specific examples of suitable binders include sugars, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, povidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium  
25 alginate, propylene glycol, and the like.

Specific examples of suitable diluents include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrates, dextrans, dextrose excipients, fructose, kaolin, lactitol,  
30 lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like.



Specific examples of suitable disintegrants include croscarmellose sodium, crospovidone and sodium starch glycolate and the like.

Specific examples of suitable surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical dosage forms. These include polyethoxylated fatty acids and their derivatives, for example, polyethylene glycol 400 distearate, polyethylene glycol – 20 dioleate, polyethylene glycol 4 – 150 mono dilaurate, polyethylene glycol – 20 glyceryl stearate; alcohol – oil transesterification products, for example, polyethylene glycol – 6 corn oil; polyglycerized fatty acids, for example, polyglyceryl – 6 pentaoleate; propylene glycol fatty acid esters, for example, propylene glycol monocaprylate; mono and diglycerides, for example, glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and their derivatives, for example, polyethylene glycol – 20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example, polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol; sugar esters, for example, sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as “poloxamer”; ionic surfactants, for example, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, palmitoyl carnitine; and the like.

Specific examples of suitable lubricants/glidants include colloidal silicon dioxide, aerosol, stearic acid, magnesium stearate, magnesium silicate, hydrogenated vegetable oils, sodium stearyl fumarate, calcium stearate, polyethylene glycol, sodium lauryl sulphate, sodium benzoate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like.

Coloring agents include any FDA colors approved for oral use.

Specific examples of suitable granulating fluids employed in the above preparations of pharmaceutical compositions include methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water, and the like.

The following examples further exemplify the invention and are not intended to limit the scope of the invention.

**Table 1.** Formulation details for Modafinil Tablets

INGREDIENT	Example #1 (mg/tablet)	Example #2 (mg/tablet)	Example #3 (mg/tablet)
<b>Intragranular Portion</b>			
Modafinil (greater than 220 $\mu$ m)	30	30	20
Modafinil (less than 220 $\mu$ m)	170 (d <sub>90</sub> 41; d <sub>50</sub> 21)*	170 (d <sub>90</sub> 23; d <sub>50</sub> 12)*	180 (d <sub>90</sub> 23; d <sub>50</sub> 12)*
Lactose	132	132	132
Starch	125	125	125
Croscarmellose Sodium	10	10	10
Povidone	10	10	10
Purified water	q.s.	q.s.	q.s.
<b>Extragranular Portion</b>			
Croscarmellose sodium	10	10	10
Colloidal silicon dioxide	5	5	5
Talc	5	5	5
Magnesium stearate	2.5	2.5	2.5

\*d<sub>x</sub>y  $\mu$ m denotes x% of particles with diameter less than y  $\mu$ m

5 Procedure for producing tablets of modafinil:

1. The modafinil particles were mixed in geometric progression with starch, lactose and intragranular croscarmellose sodium to form a blend.
2. A water solution of povidone was prepared and used for granulating the above blend to form granules.
- 10 3. The granules were dried at 60°C; sized; and mixed with extragranular croscarmellose sodium, colloidal silicon dioxide, talc, and magnesium stearate.
4. The mixture of granules and extragranular ingredients then were compressed into tablets.

As described below, between 89% and 98% of the drug was released in 60-90  
 15 minutes at 50 rpm using dissolution test apparatus USP II and water as the media wherein the drug has low solubility. The dissolution profiles of modafinil tablets prepared as per Examples 1-3 are given in Table 2.

**Table 2.** Dissolution data using USP Apparatus II, 900ml, 50rpm, water (values are indicated in cumulative percent release)

Time	Example #1 (%)	Example #2 (%)	Example #3 (%)
15 min	81	75	48
30 min	87	86	68
45 min	90	95	76
60 min	91	97	84
90 min	91	98	89

5 The dissolution data of Examples 1-3 demonstrates an ability and method to make a dosage form of modafinil in which the dissolution of the modafinil particles can be modified by varying the above ingredients to select a desired dissolution profile in which a great majority of the modafinil particles are released within 60-90 minutes. For example, 10 if there is a desire to provide a large initial release of the modafinil, e.g., within fifteen minutes, the formulations of Examples 1 and 2 are most suitable. If there is a desire to provide less of an initial release of the modafinil, the formulation of Example 3 is most suitable. As can be seen from the data in Table 2, the dissolution profile can be modified by varying the relative amounts of coarse and fine modafinil particles, as well as by 15 varying the size distribution of the fine particles.

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. For example, the oral dosage form of modafinil can be provided with labeling for one or more of 20 wakefulness promotion, to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, and idiopathic hypersomnia. Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed inventions and be so described as a negative limitation. Accordingly, it is not intended 25 that the inventions be limited, except as by the appended claims.

**We Claim:**

1. A process for preparing an oral dosage form containing modafinil, the process comprising:
  - forming a dosage form comprising
    - about 7% - 25% by weight of modafinil particles have diameters greater than 220  $\mu\text{m}$ ; and
    - about 75% - 93% by weight of modafinil particles have diameters less than 220  $\mu\text{m}$ .
2. The process according to claim 1 wherein about 7% by weight of the modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 93% by weight of the modafinil particles have diameters less than 220  $\mu\text{m}$ .
3. The process according to claim 1 wherein about 10% by weight of the modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 90% by weight of the modafinil particles have diameters less than 220  $\mu\text{m}$ .
4. The process according to claim 1 wherein about 15% by weight of the modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 85% by weight of the modafinil particles have diameters less than 220  $\mu\text{m}$ .
5. The process according to claim 1 wherein the specific surface area of the modafinil particles is at least 0.2  $\text{m}^2/\text{gm}$ .
6. The process according to claim 1 wherein the dosage form releases at least 75% of the modafinil in about 45 minutes.
7. The process according to claim 1 wherein the dosage form comprises a tablet or a capsule.
8. The process according to claim 1 further comprising one or more pharmaceutically acceptable excipients.
9. The process according to claim 8 wherein the pharmaceutically acceptable excipients comprise one or more of binders, diluents, disintegrants, surfactants, lubricants, glidants, and coloring agents.
10. The process according to claim 1 wherein forming the dosage form comprises

blending the modafinil particles with one or more pharmaceutically inert excipients to form a blend,

granulating the blend to form granules,

blending the granules with one or more pharmaceutically inert excipients, and  
compressing or filling into a solid dosage form.

11. The process according to claim 10 wherein granulating comprises wet granulation.

12. The process according to claim 10 wherein granulating comprises dry granulation.

13. The process according to claim 10 wherein the dosage form comprises a tablet and the process further comprises coating the tablet.

14. The process according to claim 1, wherein forming the dosage form comprises blending the modafinil particles with one or more pharmaceutically inert excipients to form a blend and compressing the blend or filling the blend into a solid dosage form.

15. The process according to claim 1 wherein forming a dosage form further comprises mixing the modafinil particles in geometric progression with one or more pharmaceutically acceptable excipients to form a blend.

16. The process according to claim 15 further comprising:  
granulating the blend to form granules;  
optionally drying the granules;  
sizing the granules;  
mixing the sized granules with one or more pharmaceutically acceptable excipients; and  
compressing into a tablet.

17. An oral dosage form of modafinil comprising:  
about 7% to 25% by weight of modafinil particles have diameters greater than 220  $\mu\text{m}$ ; and

about 93% to 75% by weight of modafinil particles have diameters less than 220  $\mu\text{m}$ .

18. The oral dosage form according to claim 17 wherein about 7% by weight of the modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 93% by weight of the modafinil particles have diameters less than 220  $\mu\text{m}$ .

19. The oral dosage form according to claim 17 wherein about 10% by weight of the modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 90% by weight of the modafinil particles have diameters less than 220  $\mu\text{m}$ .

20. The oral dosage form according to claim 17 wherein about 15% by weight of the modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 85% by weight of the modafinil particles have diameters less than 220  $\mu\text{m}$ .

21. The oral dosage form according to claim 17 wherein the specific surface area of the modafinil particles is at least 0.2  $\text{m}^2/\text{gm}$ .

22. The oral dosage form according to claim 17 wherein the dosage form releases at least 75% of the modafinil in about 45 minutes.

23. The oral dosage form according to claim 17 wherein the dosage form comprises a tablet or capsule.

24. The oral dosage form according to claim 17 further comprising one or more pharmaceutically acceptable excipients.

25. The oral dosage form according to claim 24 wherein the pharmaceutically acceptable excipients comprises one or more of binders, diluents, disintegrants, surfactants, lubricants, glidants, and coloring agents.

26. A method of treating a condition using modafinil, the method of treating comprising:

providing an oral dosage form of modafinil comprising

about 7% to 25% by weight of modafinil particles have diameters greater than 220  $\mu\text{m}$ ; and

about 93% to 75% by weight of modafinil particles have diameters less than 220  $\mu\text{m}$ .

27. The method according to claim 25 wherein about 7% by weight of the modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 93% by weight of the modafinil particles have diameters less than 220  $\mu\text{m}$ .

28. The method according to claim 25 wherein about 10% by weight of the modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 90% by weight of the modafinil particles have diameters less than 220  $\mu\text{m}$ .

29. The method according to claim 25 wherein about 15% by weight of the modafinil particles have diameters greater than 220  $\mu\text{m}$  and about 85% by weight of the modafinil particles have diameters less than 220  $\mu\text{m}$ .

30. The method according to claim 25 wherein the specific surface area of the total modafinil particles is at least 0.2  $\text{m}^2/\text{gm}$ .

31. The method according to claim 25 wherein the dosage form releases at least 75% of the modafinil in about 45 minutes.

32. The method according to claim 25 wherein the dosage form comprises a tablet or capsule.

33. The method according to claim 25 further comprising one or more pharmaceutically acceptable excipients.

34. The method according to claim 33 wherein the pharmaceutically acceptable excipients comprise one or more of binders, diluents, disintegrants, surfactants, lubricants, glidants, and coloring agents.

35. The method according to claim 25 wherein the condition comprises one or more of narcolepsy and idiopathic hypersomnia.

36. An oral dosage form of modafinil comprising an intragranular portion and an extragranular portion:

the intragranular portion comprising about 7% to 25% by weight of modafinil particles having diameters greater than 220  $\mu\text{m}$ , about 93% to 75% by weight of modafinil particles having diameters less than 220  $\mu\text{m}$ , and one or more pharmaceutically acceptable excipients; and

the extragranular portion comprising one or more pharmaceutically acceptable excipients.

37. The oral dosage form according to claim 36 wherein the oral dosage form releases one or more of between 48% and 81% of the modafinil within 15 minutes, between 68% and 87% of the modafinil within 30 minutes, between 76% and 95% of the modafinil within 45 minutes, between 84% and 97% of the modafinil within 60 minutes, and between 89% and 98% of the modafinil within 90 minutes.

38. The oral dosage form according to claim 37 wherein the modafinil is released in a USP Apparatus II, in 900 ml of water, and stirred at 50 rpm.

39. The oral dosage form according to claim 36 wherein the oral dosage form is provided with labeling for one or more of wakefulness promotion, to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, and idiopathic hypersomnia.



## INTERNATIONAL SEARCH REPORT

International application No

PCT/IB 03/02693

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/14 A61K9/20 A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 293 103 A (CEPHALON INC) 20 March 1996 (1996-03-20) page 4, line 7 - line 10 page 8, line 16 - line 27 page 9, line 24 - page 10, line 1 page 13, line 11 - line 18; figure 1 paragraph '000X! claim 1 & US RE37516 E 15 January 2002 (2002-01-15) cited in the application -----	1-39



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

28 October 2003

Date of mailing of the international search report

06/11/2003

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
 Fax: (+31-70) 340-3016

Authorized officer

Epskamp, S

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 03/02693

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 26-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: .
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No

PCT/IB 03/02693

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 2293103	A	20-03-1996	US 5618845 A	08-04-1997
			AT 188607 T	15-01-2000
			AT 199216 T	15-03-2001
			AU 3509099 A	19-08-1999
			AU 703087 B2	18-03-1999
			AU 3951495 A	02-05-1996
			BG 62952 B1	29-12-2000
			BG 101389 A	30-12-1997
			BR 9509257 A	07-07-1998
			CA 2201967 A1	18-04-1996
			CA 2382275 A1	18-04-1996
			CZ 9701032 A3	17-09-1997
			DE 69514497 D1	17-02-2000
			DE 69514497 T2	10-08-2000
			DE 69520161 D1	29-03-2001
			DE 69520161 T2	02-08-2001
			DK 731698 T3	08-05-2000
			DK 966962 T3	19-03-2001
			EE 9700082 A	15-10-1997
			EP 1088549 A1	04-04-2001
			EP 0731698 A1	18-09-1996
			EP 0966962 A1	29-12-1999
			ES 2142499 T3	16-04-2000
			ES 2156457 T3	16-06-2001
			FI 971417 A	04-04-1997
			GR 3033152 T3	31-08-2000
			GR 3035451 T3	31-05-2001
			HK 1024625 A1	28-09-2001
			HK 1003561 A1	30-10-1998
			HU 77778 A2	28-08-1998
			JP 2915146 B2	05-07-1999
			JP 9511754 T	25-11-1997
			KR 249360 B1	01-04-2000
			LT 97060 A ,B	27-10-1997
			LV 11852 A	20-10-1997
			LV 11852 B	20-03-1998
			NO 971541 A	04-06-1997
			NZ 295869 A	26-02-1998
			PL 319480 A1	04-08-1997
			PT 731698 T	31-05-2000
			PT 966962 T	29-06-2001
			SI 9520106 A	28-02-1998
			SK 44597 A3	10-09-1997
			WO 9611001 A1	18-04-1996
			US RE37516 E1	15-01-2002